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32 PHARMACOLOGICAL THERAPY

"We must recollect that all our provisional ideas in psychology will some day be based on an organic substructure. This makes it probable that special substances and special chemical processes control the operation. . ."

Sigmund Freud

J. P. L. DELAY

Codiscoverer (with P. Deniker) of tranquilizing effects of chlorpromazine.

(From Kline, N. S.: Psychopharmacology Frontiers. Boston, Little, Brown & Company, 1959. And: International Congress of Psychiatry, 2nd, 1957. Proc. of the Psychopharmacology Symposium, p. XIII.)

For the treatment of the most severe mental disorders, psychotropic drugs are the primary therapeutic agents. Certain of these drugs are useful in providing symptomatic relief in the psychoneuroses and physiological disturbances, while others act specifically in relation to certain symptoms, or are useful as enhancers for the effects of other drugs.

The agents now well recognized as modifying pathological behavior may be classified into the neuroleptics, the antidepressants, the anxiolytic sedatives, the psychostimulants, and the somnifacients. The classification in Table 32–1 is based on the recommendation of the Special Committee of the World Health Organization.

The neuroleptics modify psychotic behavior in general and have become the major therapeutic agents, particularly in the treatment of the schiz-

TABLE 32–1 Classification of Psychotropic Drugs Used Therapeutically

CATEGORY	REPRESENTATIVE MEMBERS
Neuroleptics	Phenothiazines Butyrophenones Thioxanthenes Dihydroindolines Dibenzoxazepines Rauwolfia alkaloids
Antidepressants and affective modulators	Monoamine oxidase (MAO) inhibitors Tricyclic compounds Lithium compounds
Anxiolytic sedatives	Glycerols Diphenylmethanes Benzodiazepines
Psychostimulants	Amphetamine, methylphenidate, dibenzoxepin Caffeine
Somnifacients	Barbiturates Chloral Hydrate Ethchlorvynol Flurazepam Glutethimide Methyprylon Methaqualone Paraldehyde

(Modified, updated, and expanded from the classification recommended by the Special Committee of the World Health Organization, 1967.)

ophrenias. The neuroleptics have the capacity to modify affective states without seriously impairing cognitive functions. In this respect, they differ from the somnifacient drugs. In addition to their reaction upon the central nervous system in modifying behavior, they affect the functioning of the extrapyramidal nervous system and the autonomic system. Generally, they act by blocking dopamine receptors in the brain. Included in the group are the phenothiazines, the butyrophenones, the dihydroindolines, the dibenzoxazepines, and the rauwolfia alkaloids.

The antidepressants are complex agents, with pharmacological effects in particular on the biogenic amines norepinephrine and serotonin. They include the tricyclic compounds and the hydroxide and nonhydroxide monoamine oxidase inhibitors.

The cerebral stimulants include the dextroamphetamines and methylphenidate. These agents tend to produce a transient increase in psychomotor activity. They must be considered as stimulants and are not effectively antidepressant. However, they enhance the activity of certain of the antidepressants.

The anxiolytic agents are sedative hypnotics that generally depress brain function. Pharmacologically, they do not affect the extrapyramidal or the autonomic nervous systems, as do the neuroleptics. Benzodiazepines are the most frequently prescribed drugs in this class. These drugs are more frequently prescribed than any other in America. Although they were thought to exert their psychotropic effects through action on the GABA or glycine neurotransmitter systems, it has recently been shown that human brain con-

tains receptors for benzodiazepines. Thus, the possibilities exist that these drugs act by direct stimulation of receptors, and that the brain may synthesize compounds quite similar to the benzodiazepines.

Individuals receiving these agents develop a tolerance and may become habituated or addicted or both. Because of the possibility of addiction, they have been classified in many countries as controlled substances.

The somnifacients include the well-known barbiturates, chlorohydrate, ethchlorvynol, glutethimide, methyprylon, methaqualone, and flurazepam. Pharmacological effects are generally of shorter duration and are more intense than those of the anxiolytic drugs.

The anticholinergic agents are significant as they are effective in the treatment of drug-induced parkinsonism, so common in administration of the neuroleptics.

Since it is expected that the able psychiatrist comes to practice fully knowledgeable from previous medical studies of the well-known properties of and clinical indications for using central nervous system depressants such as the narcotics, anesthetics, hypnotics, and intoxicants, as well as the stimulants, consideration is not given to these drugs in this text. Their skillful prescription, often in conjunction with that of the neuroleptics, is demanded in practice.

PHARMACOLOGICAL ACTION AND BRAIN FUNCTION

The active psychotropic drugs exert complex actions upon various neural systems and the neuron itself. These actions have been demonstrated through changes brought about in animal behavior (particularly through analysis of responses obtained by classical and instrumental conditioning), through depth electroencephalography, through electrophysiological and biochemical studies of synaptic transmission, and through studies of drug metabolism within bodily tissues and changes in endocrine functions.

It is well known now that the psychotropic drugs have a long half-life in bodily fluids. The drugs and their metabolites accumulate in bodily tissues as administration is continued over time. This accumulation ceases when the saturation level is achieved. With cessation of administration, the tissues slowly release the accumulated drugs. Thus, traces may be found in the urine for two or three months after discontinuance. The psychopharmacological properties are generally manifest days to weeks later than the early effects on the other segments of the central nervous system. Thus, the side effects frequently precede the therapeutic response. These well-recognized pharmacodynamic properties are most important, particularly in relation to the modes of administration, prescription, and assessment of therapeutic response, as will be described.

Much of the variation in effect produced by the differing agents is thought to depend upon their differing actions at the synaptic junctions within the brain. It is considered that the passage of a nerve impulse from activated neurons takes place across the synaptic junction by discharge into the synaptic cleft of the neurotransmitters. These substances then activate the receptors of the postsynaptic neuron.

In Chapter 3 (The Brain and Behavior) and Chapter 18 (Schizophrenic Disorders), respectively, the synaptic action of the various biogenic amines and the "dopamine hypothesis" as it relates to schizophrenia were described. Norepinephrine, dopamine, the indoleamine serotonin, gamma-aminobutyric acid or acetylcholine are differentially disposed through the brain stem. Certain pathways have been identified as principally containing and thereby activated by dopamine and noradrenaline (Fig. 32–1).

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